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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/275,883	03/25/99	RENNER	W 1700.0020001

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EXAMINER

SCHNIZER, R

ART UNIT	PAPER NUMBER
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1632

DATE MAILED:

01/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/275,883

Applicant(s)

RENNER ET AL.

Examiner

Richard Schnizer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 November 2000.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 75-125 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 102 is/are allowed.
- 6) ☒ Claim(s) 75-101 and 103-125 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____.

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DETAILED ACTION

An amendment was received and entered as Paper No. 14 on 11/15/00. Claims 1-74 were canceled and new claims 75-125 were added as requested. In paper No. 10 applicant elected the species of DNA molecules wherein the second open reading frame encoded erythropoietin. Claims 85 and 108 do not encompass this elected species and are withdrawn from further consideration as being drawn to non-elected subject matter. Claims 75-125 are pending in the application, and claims 75-84, 86-107, and 109-125 are under consideration in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 75-84, 86-101, 103-107, and 109-125 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons applied to claims 1-4, 6, 8-14, 16-34, 38-70, and 74 in Paper No. 11.

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Applicant's arguments filed 11/15/00 have been fully considered but they are not persuasive.

The claimed invention encompasses the genus of DNA molecules comprising an open reading frame encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase. The specification discloses a single example of an open reading frame encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase.

Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at www.uspto.gov). The following passage is particularly relevant.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, *i.e.* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The central issue in this analysis of compliance with the written description requirement is whether Applicant has disclosed a number of species which is representative of the claimed genus. Applicant discloses a single open reading frame encoding a Sindbis virus RNA-dependent RNA polymerase. This polymerase comprises a P726S nsP2 mutation in combination with a G153E

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nsP4 mutation. The P726S nsP2 and G153E nsP4 mutations are the structural features which are required to render the Sindbis virus polymerase both temperature sensitive and non-cytopathic. See paragraph bridging pages 21 and 22; page 22, lines 17 and 18; and page 23, lines 22-24. Temperature sensitivity and non-cytopathicity are the necessary common attributes which the polymerase must possess in order to qualify as a member of the claimed genus. However, the specification has failed to disclose what mutations are required to render any other RNA-dependent RNA polymerase both temperature sensitive and non-cytopathic, or what other mutations could confer this phenotype on the Sindbis virus. The state of the art of the prediction of protein function based on protein structure is not sufficiently advanced to predict *a priori* what mutations will confer temperature sensitivity or non-cytopathicity on a given RNA-dependent RNA polymerase, so it falls to the specification to provide this information. One of skill in the art appreciates that a wide variety of RNA-dependent RNA polymerases is known in the art. In view of this recognized variety, and in view of the uncertainty associated with predicting which amino acid substitutions will confer temperature sensitivity and non-cytopathicity on a given polymerase, the disclosure of only a single species is considered insufficient to convey to one of skill in the art that applicant was in possession of the claimed genus at the time of the invention.

Applicant's contention that the description requirement may be met by the disclosure of a single species is correct, but only in situations where a single species is provides representative example of the common attributes which are required of the genus. In this case, the mutations disclosed cannot be considered to be applicable to any polymerase other than Sindbis virus

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polymerase. The specification fails to teach what corresponding mutations must be made in RNA-dependent RNA polymerases from other sources in order to achieve temperature sensitivity and non-cytopathicity.

Applicant also argues that more than one species has been disclosed because more than one non-identical nucleic acid comprising the claimed polymerase is described in the specification. However, these examples consist only of the single disclosed polymerase open reading frame associated with other nucleic acids such as marker proteins, erythropoietin, *etc*; degenerate forms of these nucleic acids which encode the same polypeptides; and other genetic elements such as subgenomic promoters. Again, only a single species of the claimed genus of polymerases is disclosed in the specification. The disclosure of nucleic acids comprising this open reading frame associated with other open reading frames or genetic elements does not constitute the disclosure of more than one species of RNA-dependent RNA polymerase.

Finally, Applicant argues that the instant claims are similar to example 14 of the written description guidelines, which serves as an example of a claim which satisfies the written description requirement. This is unpersuasive because the genus claimed in example 14 is limited to proteins which have 95% sequence identity to a disclosed sequence. The instant claims have no such limitation, rather they encompass any RNA-dependent RNA polymerase which is temperature sensitive and non-cytopathic. Applicant is in possession of only a single example of this genus. For this reasons, and those given above, the rejection is maintained.

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Enablement

Claims 75-84, 86-101, 103-107, and 109-125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use in BHK-21 cells *in vitro* of nucleic acid molecules encoding a heterologous open reading frame and a Sindbis virus non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase with P726S nsP2 and G153E nsP4 mutations, wherein the heterologous open reading frame is operatively linked to a promoter recognized by Sindbis virus RNA-dependent RNA polymerase, does not reasonably provide enablement for the use of these nucleic acids in any other cell type *in vivo* or *in vitro*, or for the use of any other nucleic acid which lacks a promoter recognized by Sindbis virus RNA-dependent RNA polymerase, or which encodes any other non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, in any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons of record in Paper No. 11.

The invention encompasses nucleic acid molecules encoding a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase and methods of using the nucleic acids. The molecules also encode an open reading frame which must undergo at least one RNA-dependent RNA polymerase-mediated replication event in order to be translatable. Claims 86, 93-101, 109, and 116-125, are methods of using the nucleic acids of the invention either *in vivo* or *in vitro*. The specification asserts no utility for using these nucleic acids *in vivo* other than gene therapy. The specification fails to enable the general practice of gene therapy for the reasons

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given in Paper No. 11. Briefly, the art of gene therapy is highly unpredictable, known delivery and expression systems are inadequate for therapeutic purposes, and the instant specification fails to complement the deficiencies of the prior art. Applicant has not rebutted these arguments. Rather, Applicant argues that because the nucleic acids can be used *in vitro*, there is at least one enabled utility, and this is sufficient to meet the enablement requirement. Applicant is reminded that composition claims require only a single enabled utility, whereas method claims must be enabled across the breadth of the claimed scope. In light of the instant specification, at page 1, lines 17-19, and pages 33-37, methods of gene therapy are encompassed in the claimed methods. In order to overcome this portion of the rejection, it is suggested that claims 86, 93-101, 109, and 116-125 should be specifically limited to *in vitro* methods.

As discussed above, the specification discloses only a single example of a non-cytopathic, temperature-sensitive RNA-dependent RNA polymerase, yet the claims encompass the entire genus rather than just the single disclosed species. Applicant argues that one of skill in the art would have been able to construct other polymerases from existing material known in the art without undue experimentation. Specifically, the prior art teaches several Sindbis virus polymerases which are temperature sensitive, and several other Sindbis virus polymerases which are non-cytopathic. However, Applicant fails to disclose any example, other than that encoded by SEQ ID NO:1, of a polymerase which is both temperature sensitive **and** non-cytopathic. While it is simple to construct nucleic acids which would comprise both types of mutations, the characteristics of these novel polypeptides would be highly unpredictable, as stated in the previous

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office action. The reason for this is that it is not currently possible to accurately predict the effects of mutations on the function of proteins. For example, Rudinger (In Peptide Hormones, J.A. Parsons Ed. University Park press, Baltimore, 6/1996) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." See page 6, last paragraph. Furthermore, Schnizer et al (Arch Biochem Biophys. 1996 Feb 1;326(1):126-36) teach an example in which mutations of two separate amino acids of the yeast F1-ATPase beta subunit were combined and produced totally unpredictable results. Specifically, one mutation at position 203 and four different mutations at position 211 were found to inactivate and destabilize the F1-ATPase complex when expressed separately. However, when the position 203 mutation was combined with any one of the position 211 mutations in the same construct, destabilization was suppressed and activity was restored to the ATPase complex. See abstract. While this result may allow certain conclusions to be drawn about structural and functional relationships within the ATPase, it could not have been predicted *a priori*. Similarly the effects of combining mutation in the Sindbis virus polymerases cannot be predicted *a priori*. One might argue that it would not be undue experimentation to express and assay each construct individually and thereby determine empirically which ones encoded polymerases of the desired phenotype. However, as set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

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that scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with degree of unpredictability of factors involved.

Emphasis added. In this case, the art is not sufficiently advanced to allow the prediction of the effects of combining these mutations. Furthermore, Applicant has disclosed mutations only of Sindbis virus polymerases, whereas the claims encompass RNA-dependent RNA polymerases from all sources. One of skill in the art could not predict which, if any, of these polymerases could be mutated to be appropriately temperature sensitive **and** non-cytopathic, or what mutations would be required for this.

Applicant argues that the enablement requirement is fulfilled with respect to range of host cells encompassed by the claims if one of skill in the art is able to identify cells without undue experimentation that are suitable for practicing the claimed invention. Applicant asserts that the inventor is prepared to submit a declaration averring that 9 mammalian cell lines in addition to BHK-21 cells will support replication of the claimed nucleic acids. Applicant is advised that if this declaration shows that the nucleic acids function in a non-cytopathic, temperature-sensitive manner in these cells, then it will be sufficient to enable the host range of mammalian cells *in vitro*.

Applicant's arguments that a random search for suitable cell lines is not undue experimentation are unconvincing. The comparison to the screening of monoclonal antibodies is inappropriate because monoclonal antibody technology is well established whereas the

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identification of cell lines which support the replication of the novel claimed polymerases is not. As stated before, Agapov was surprised by, and unable to explain the limited host range conferred by the position 726 mutation, and went on to suggest that unknown obstacles to replication must be overcome before host range can be expanded. The identification of these obstacles represents undue experimentation. Random screening of cell lines is not an acceptable solution, because, it is unknown if such cell lines exist. In contrast, screening for monoclonal antibodies is routine, and in situations where it appears that an antibody has not been raised, there are established techniques for improving the antigenicity of an antigen and the immune response of the mouse, *e.g.* the use of haptens and adjuvants.

Applicant notes that the host cell range presented in Agapov may not correlate with that of the vectors of the instant application because the vectors are not identical, and then relies on Agapov's demonstration of replication in two cell lines other than BHK-21 as evidence for enablement in cells other than BHK-21. Agapov was relied on by the examiner to demonstrate that it is difficult to predict which cell lines will support replication by a virus comprising non-cytopathic polymerase. The instant invention is similar to the vector of Agapov in that position 726 of the polymerase is mutated to cause a non-cytopathic phenotype. However, it differs in that it comprises a second site mutation, and in that the mutation at the position 726 mutation is a serine substitution, rather than the leucine substitution of Agapov. Because Agapov finds that a noncytopathic vector with a mutation at position 726 has a limited host range, there is reasons to suspect that the vector of Applicant may have a limited host range as well, particularly in the

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absence of any evidence to the contrary. Because the instant vector is not identical to that of Agapov, it is not known if it will be active in the same cells. The specification reports replication in only a single cell type, so it is reasonable to limit the claims to that cell type in view of the unpredictability of the subject matter.

Applicant's arguments regarding the use of promoters not recognized by Sindbis virus RNA-dependent RNA polymerase are unpersuasive. The essence of the rejection is that, because the specification has disclosed only a single polymerase with the attributes required by the claims, the claimed vector must comprise a promoter which is recognized by that polymerase. Applicant provides no evidence that any promoter is recognized by the disclosed polymerase other than the promoter carried by SEQ ID NO:1. In this regard, the alignment disclosed by Strauss does not constitute evidence that the polymerase of the instant invention will recognize and bind to any other promoter. It is not disputed that one of skill in the art could construct vectors comprising promoters recognized by other RNA-dependent RNA polymerases. The issue is whether or not any of these promoters would be recognized by the single polymerase that applicant has disclosed.

For all of these reasons the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 75-101 and 103-125 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 75-101 and 103-125 are indefinite because these claims require "a promoter which is activated by" a polymerase.

Conclusion

Claim 102 is allowed. All claims are free of the prior art of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441.

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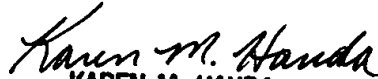
The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Questions regarding formal matters may be directed to the Patent Analyst, Patsy Zimmerman, whose telephone number is 703-305-2758.

Richard Schnizer, Ph. D.


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